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Review article

An update on the mechanisms of Takotsubo syndrome: "At the end an acute coronary syndrome"

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ABSTRACT

Takotsubo syndrome (TTS) is an acute reversible form of myocardial dysfunction, often preceded by a physical or emotional stressful event, that acts as a trigger. Despite, recent advances in the comprehension of the mechanisms leading to TTS, its pathophysiology is far from being completely understood. However, several studies seem to suggest that an acute coronary microvascular dysfunction may represent a crucial pathogenic mechanism involved in TTS occurrence.

In this article, we aim to review the complex pathophysiology of TTS and the possible different mechanisms underlying this clinical condition, focusing on the role of coronary microvascular dysfunction and the remaining knowledge's gaps in the field.

1. Introduction

Takotsubo syndrome (TTS) is a clinical condition characterized by a reversible left ventricular (LV) dysfunction, often preceded by a physical or emotional stressful event, that acts as a trigger [1]. TTS is characterized by peculiar LV wall motion abnormalities extended beyond a single epicardial coronary artery distribution and in absence of a "culprit" lesion at cardiac catheterization (although it can coexist with obstructive coronary artery disease), usually presenting with apical hypokinesia/akinesia and basal hyperkinesia ("apical ballooning") [2–5]. Less frequently, wall motion abnormalities affect the mid-ventricular or basal regions or focal segments [6]. Even though it has been traditionally considered as a benign condition for its self-limiting nature, recent data have clearly demonstrated that haemodynamic and electrical instability during the acute phase of TTS may expose patients to a relevant risk of mortality and acute life-threatening complications, similar to patients with acute coronary syndromes (ACS) due to coronary artery disease (CAD), and to a non-negligible risk of recurrence [4,6–8]. Nevertheless, the pathophysiology of TTS is far from being completely understood.

In this article, we aim to review the complex pathophysiology of TTS and the possible different mechanisms underlying this clinical condition, focusing on the role of coronary microvascular dysfunction and the remaining knowledge's gaps in the field.

2. Triggers and predisposing factors

2.1. The Cardio-neuro axis and the pathophysiological response to stress

Up to two-third of patients presenting with TTS report a recent environmental event perceived as stressful (either physical or emotional) [6]. Emotional triggers often include the death of a loved one, natural disasters, financial troubles, and even sexual abuse. On the other hand, physical stressors causing TTS may include a previous surgery, central nervous system conditions, acute respiratory failure and trauma [6]. The evidence of a stressful event preceding the outbreak of TTS, the higher prevalence of neurological disorders (e.g. intracranial bleeding, seizures and migraines) and pre-existing psychiatric disorders in patients with TTS supports the notion of an outstanding link between the brain stress response system and the heart in the pathogenesis of this syndrome [6,9].

A pivotal study by Wittstein et al. documented for the first time extremely high levels of plasma catecholamines (epinephrine, norepinephrine and dopamine) and stress-related neuropeptides (e.g. the neuropeptide Y) in patients with TTS compared to Killip class III ACS patients, suggesting a direct causal link between plasma catecholamines and TTS [10]. Further revisions of these findings and recalculation of the plasma epinephrine levels in Wittstein's study revealed only a modest increase of plasma epinephrine, thus challenging the hypothesized

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central role of catecholamines in TTS pathogenesis [11]. Interestingly, a more relevant increase in norepinephrine has been detected in the coronary sinus compared to the aorta during the acute phase of TTS, which suggests that local rather than circulating catecholamines levels may be crucial for disease onset [12]. Of note, both cardiac catecholamine-producing enzymes and sympathetic nervous fibers are predominantly left-sided and present a differential distribution from base to apex, which may account for the typical wall motion regional abnormalities in TTS [13,14].

Recently, the use of advanced neuroimaging techniques convincingly demonstrated the presence of anatomical and functional heart-brain connections, which may play a key role in the pathogenesis of TTS.

The fundamental anatomic structures involved in the stress response are the neocortex, limbic system, reticular formation, brainstem, and spinal cord along with the hypothalamic-pituitary-adrenal axis which finally leads to cortisol secretion. Substantial differences in the neocortex and the limbic network have been documented in TTS patients using brain functional magnetic resonance imaging (fMRI). Templin et al. described altered structural connectivity patterns and reduced activation during resting state in both the parasympathetic (right amygdala, hippocampus, middle and superior temporal gyrus, left motor cortex, left supramarginal/angular gyrus, and the left cerebellum) and the sympathetic subnetworks (left and right amygdala, cingulate gyrus, left dorsolateral prefrontal cortex, left and right cerebellum, and the left superior parietal lobule/supramarginal gyrus) of patients with a prior TTS [15,16]. In addition, the authors documented a hypo-connectivity in the brain regions holding the "default mode network" (i.e. hippocampus, prefrontal cortex, posterior cingulate cortex, left temporal pole, bilateral posterior inferior parietal lobule, and the left and right temporoparietal junction), a functional structure involved in making certain self-relevant decisions [11]. Therefore, in the presence of a stressful event, the impaired default mode network subsystems may lead to a more pessimistic evaluation of the present and future self and to a higher level of stress that may be responsible for the development of the TTS.

However, as these findings by Templin et al. have been observed in individuals with prior TTS, they raised the key question of whether such changes were the cause or the result of TTS.

A more recent positron emission tomography/computed tomography (PET/CT) study addressed this question by demonstrating that the heightened activity of the amygdala and the stress related response system precedes by years the development of the clinically manifested TTS, and that patients with the highest activity of the amygdala develop the syndrome earliest [17]. In addition, Suzuki et al. reported a higher activity of the amygdala at PET in 4 patients during the acute phase of TTS as compared with recovery phase [18]. Hence, heightened basal and acute amygdala activation may predispose individuals to TTS by potentiating the sympathetic, neurohormonal, and inflammatory consequences of events perceived as stressful.

However, the presence of predisposing cortical alterations may only partially explain the reason why TTS occurs only in a portion of individuals after a stressful event. Other clinical conditions resulting in an increased central sympathetic drive (i.e. postmenopausal state, asthma/chronic obstructive lung diseases, underlying myocardial diseases) have been proposed as possible contributors in the pathogenesis of TTS. Of interest, diabetes mellitus has been recently investigated as possible pathogenetic contributor to TTS as it is known to induce neuro-autonomic nerve remodeling and an upregulation of vasoactive neuropeptides (i.e. neuropeptide Y [NPY]) involved in the myocardial autonomic modulation [19,20]. In particular, Stiermaier et al. evaluated the prevalence and prognostic significance of type 2 diabetes mellitus (T2DM) in TTS patients using the multicenter international German Italian Stress cardiomyopathy (GEIST) registry, demonstrating that T2DM was frequent, ranging up to 21% in the population cohort and that patients affected had a higher all-cause mortality compared with patients without T2DM (31.4% vs. 16.5%; $p < 0.001$) [19]. Further studies have confirmed the relative high prevalence of this clinical condition in individuals with TTS, supporting the possible causative role of DM in its pathogenesis [20]. Since TTS has been identified in an increasing number of hospitalized patients, an important clinical heterogeneity emerged among affected individuals. In particular, clinical characteristics such as physical triggers along with acute neurologic or psychiatric disease, high troponin levels, and lower LV ejection fraction showed to identify a specific group of individuals with TTS at higher risk of mortality and in-hospital complications [1]. Therefore, it has been hypnotized that we have so far described two different subsets of TTS patients, with different clinical features and risk profiles: a "primary TTS", which mainly affects postmenopausal females after an emotional stressor with minor troponin release, slightly reduced and rapidly reversed LV dysfunction and benign prognosis; a "secondary TTS", occurring after a physical stressor also in male patients, with major troponin release, more severe or persistent LV dysfunction and associated with worse prognosis [21].

2.2. Hormone deficiency and dysregulation

Most patients with TTS are postmenopausal women [6]. Therefore, oestrogen deficiency has been proposed as a possible pathogenetic mechanism of SCMP. Oestrogens have several protective effects on the cardiovascular system, that are principally attributed to the modification of serum lipid concentration and coagulation pathways, and to the protective effects on endothelial function [22]. These effects are mediated by the presence of estrogenic receptors (ERα and ERβ) in the blood vessels and in the heart. Both ERαand Erβ are also widely expressed in the central nervous system, where oestrogens play crucial roles in behaviour and autonomic nervous function modulations [23]. Therefore, a reduction of estrogenic levels following menopause might increase the susceptibility of women to stress, while oestrogens supplementation might attenuate the exaggerated response to stress. This hypothesis has been confirmed in an elegant experimental study by Ueyema et al., demonstrating that in an animal model of TTS LV dysfunction can be prevented by pretreatment with oestrogens administration [24]. Moreover, the administration of oestrogens has been shown to reduce the activation of the sympathetic-adrenal glands axis, leading to a lower production and spillover of catecholamines [24]. In addition, because estrogenic receptors are also expressed in the cardiac cells, oestrogens can directly act to reduce the heart reactivity to catecholamines either by upregulating the cardiac levels of cardioprotective substances (i.e. atrial natriuretic peptide and heat shock protein 70) and by antagonizing the upregulation of the β1-adrenergic receptor often observed in TTS [24,25].

Finally, under physiological circumstances, oestrogens proved to act beneficially to the coronary microcirculation via endothelium-dependent and -independent mechanisms, thus preserving the microcirculatory homeostasis and improving coronary blood flow [24,26–28]. Indeed, in animal models oestrogens administration was proved to reverse the coronary constriction induced by acetylcholine infusion via an endothelium-dependent action. On the other hand, the infusion of oestradiol-17 showed to induce a direct coronary vasodilatation not prevented by de-endothelialization, nor by nitric oxide synthase or cyclo-oxygenase inhibition, thus suggesting an endothelial-independent effect of the hormone [28].

These data suggest that oestrogens deficiency after menopause might facilitate the occurrence of TTS, in particular TTS linked to an emotional trigger, either by a direct action on the heart and on the coronary circulation, and by the loss of a regulatory and protective function on the nervous system.

2.3. Genetic predisposition and epigenetic factors

The suspect of a genetic predisposition to develop TTS has been raised by the evidence of both personal susceptibility to TTS occurrence

and relapse and of cases running in the same family [29–32]. However, the studies conducted with a view to ascertain this hypothesis have provided conflicting results. Considering that the most common characteristic among TTS patients is an adrenergic hyperactivity, most studies focused on the genes involved in the adrenergic response. Among these, the genes encoding the B1 (ADRB1), B2 (ADRB2) and alpha 2c (ADRA2C) adrenergic receptors have been largely investigated, because of the different cardiac response to catecholamines according to their variants. Sharkey et al. did not find any difference in their polymorphisms frequency between a cohort of 41 TTS patients and controls [33]. On the other hand, another study evaluating the same polymorphisms reported a higher frequency of a specific ADRB2 polymorphism in TTS patients in comparison with healthy controls [34]. Spinelli et al. did not find associations of genetic polymorphisms in ADRB1, ADRB2, GNAS, GRK5 genes with TTS, with the only exception of a variant of the GRK5 gene, confirmed by Novo et al. but not by Figtree et al. [35–37]. Interestingly, Vriz et al. found different polymorphism distribution in ADBR1 and ADBR2 genes between TTS patients and controls, not evidenced when TTS and STEMI patients were compared [38].

Small studies have also explored specific variants of genes encoding for oestrogen receptors and oxidative stress mediators, but further evidence coming from larger studies is needed to confirm these data [39,40].

In reason of the inconclusive findings on polymorphisms, some groups focused on genome-wide association study, Whole exome sequencing (WES) and Next Generation Sequencing (NGS) technology. These studies suggested the possible role of several genetic loci, thus endorsing the hypothesis of a polygenic inheritance of TTS predisposition [41–43].

More recently, a growing body of evidence highlighted peculiar epigenetic alterations in the TTS population. For instance, Khurana et al. showed a cardioprotective activity of Suberanilo-hydroxamic acid (SAHA), probably due to an epigenetic (acetylation/deacetylation) axis [44].

In addition, Jaguszewski et al. found a different microRNAs (miRs) expression between patients with TTS and acute myocardial infarction, with miR16 and 26a more prevalent in TTS patients, as lately confirmed in a preclinical study [45,46]. Interestingly, these miRs have also been detected in circulation in stress, depression, and anxiety conditions, well known TTS triggers [47,48].

2.4. *Inflammation and metabolic remodeling*

Several studies reported a pro-inflammatory milieu in TTS patients, thus suggesting that inflammation could represent an adjunctive TTS trigger. Subjects with TTS during follow-up have higher serum IL-6 and IL-10 before the event and IL-6 levels are also related to LV dysfunction and clinic presentation [49]. Conversely, IL-7 seems to increase 2–4 days after admission [50,51].

Santoro et al. compared the circulating levels of several inflammatory and anti-inflammatory molecules in TTS and ACS during the acute and subacute phase and found that in the acute phase, several circulating interleukin levels were higher in subjects with TTS (such as IL-2 2, IL-4, IL-10, TNF-α, IFN-γ, EGF) compared to ACS patients, while IL-6 levels were higher in patients with ACS [52]. In the subacute phase, IL-2 and EGF levels were still higher in patients with TTS compared to ACS, while IL-6 serum levels were higher in ACS patients compared to TTS. This study suggests that different inflammatory patterns can be observed during the acute and subacute phase of TTS when compared to ACS. In particular, increased levels of anti-inflammatory interleukins can be found during the acute phase of TTC while ACS is featured by higher levels of IL-6 during the acute and sub-acute phase.

The presence of an inflammatory pattern in TTS patients has also been revealed in a cardiovascular magnetic resonance (CMR) study [53]. In addition, the link between TTS and inflammation is further endorsed by the increased susceptibility observed in subjects with autoimmune diseases [54].

Inflammation, together with sympathetic hyperactivity, is also deemed responsible for the “metabolic remodeling” occurring in the acute phase of TTS, characterized by impaired oxidative metabolism, catabolic-anabolic imbalance and insulin resistance [55,56]. Some authors suggested that the protraction of these cardiometabolic anomalies may lead to myocardial fibrosis with consequent development of heart failure with preserved EF in this population [56,57].

3. The key role of acute coronary microvascular dysfunction

The link between an acute coronary microvascular dysfunction (CMD) and TTS has been profusely investigated over the last two decades. However, whether CMD is the leading mechanism or an epiphenomenon of TTS has been a matter of intense debate [58].

A study by Galiuto et al. was the first to show that microvascular coronary spasm is the final common pathway leading to TTS [59]. They enrolled TTS patients who underwent myocardial contrast echocardiography at baseline, during adenosine infusion (140 microg/kg/min) and at 1-month follow-up and were compared with a group of anterior ST-elevation myocardial infarction (STEMI) patients with similar clinical characteristics. At baseline, no difference in myocardial perfusion and dysfunction were present between the two groups. During adenosine challenge, while no changes were observed in STEMI group, in TTS patients' parameters of myocardial perfusion and wall motion abnormalities improved significantly compared with baseline while LVEF significantly increased. At 1-month follow-up, myocardial perfusion and dysfunction completely recovered in TTS patients, whereas no significant changes were observed in STEMI group. Thus, this study showed that CMD is not secondary to myocardial dysfunction as proposed by others while it proves the opposite [58,60,61].

Recent enlightening evidence moved the needle towards the notion that acute CMD is, indeed, the last common pathway leading to TTS. Indeed, angiographic studies showed reduced TIMI (Thrombolysis In Myocardial Infarction) frame count in the majority of TTS patients, mainly encountered in the left anterior descendant (LAD) territory [62,63]. More recently, an interesting observational prospective study by Ekenbäck et al. assessed coronary microvascular function at coronary angiography using the index of microcirculatory resistance, coronary flow reserve and resistive reserve ratio in TTS and in patients affected by ischemia with non-obstructed coronary arteries (INOCA) [64]. As a result, CMD was proven to be more common in TTS and more severe in the apical compared with the midventricular phenotype.

Dong et al. conducted an elegant preclinical study in a murine CMD model in order to investigate the link between microvascular coronary flow regulation and TTS onset and treatment [65]. Wild Type (WT), Kv1.5 −/− and TgKv1.5 −/− (Kv1.5 −/− with smooth muscle-specific expression Kv1.5 channels) mice were studied following a hypertensive stress through transaortic constriction (TAC). Vascular Kv1.5 channels play a role in connecting blood flow to metabolism in the heart, and deletion of Kv1.5 channels impairs coronary metabolic dilation. For this reason, Kv1.5 −/− with TAC were used as TTS model and Kv1.5 −/− without TAC as control group. Furthermore, measurements of left ventricular (LV) function in base and apex, and myocardial blood flow (MBF) were completed with standard and contrast echocardiography. Finally, RNA deep sequencing was performed on LV apex and base from WT and Kv1.5 −/− (control and after TAC). In this study, the authors found that TAC induced TTS with systolic apical ballooning in Kv1.5 −/− mice, which was not observed in WT or TgKv1.5 −/−. In Kv1.5 −/− mice with TTS, MBF was lower in the LV apex compared to base. Of interest, MBF increased with either chromonar or smooth muscle expression of the Kv1.5 channel with normalized perfusion and function between the LV apex and base. Moreover, some genetic changes during TTS were reversed by chromonar suggesting that, at least in part, changes in gene expression were independent of TAC.

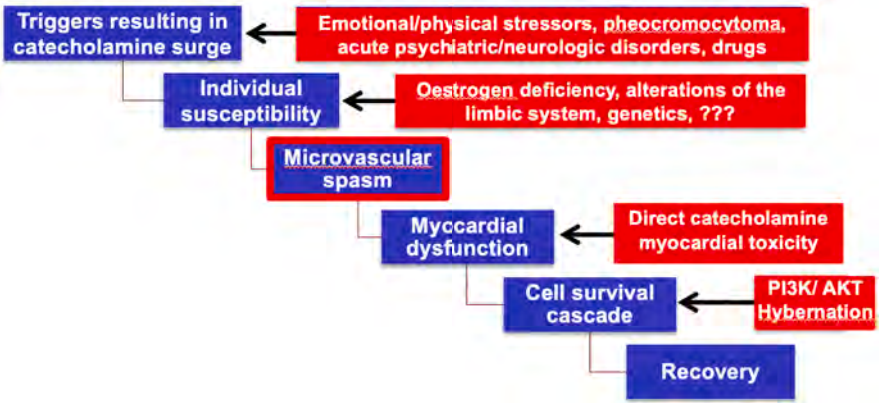

Fig. 1. A novel proposal for Takotsubo pathophysiology.
This figure depicts our novel proposal for Takotsubo (TTS) pathophysiology. Emotional and physical triggers act on a predisposing soil, including female sex, peculiar genetic and epigenetic background. These factors promote cardio-neuro axis activation, hormonal dysregulation, exaggerated inflammatory response and metabolic remodeling, all fostering acute microvascular dysfunction and, ultimately, TTS onset.

Table 1
Studies evaluating acute microvascular dysfunction in Takotsubo Syndrome.

Reference	Study population/ Protocol	Methodology	Results
Ekenbäck et al. [54]	27 female TTS patients 27 age and gender-matched INOCA patients	Coronary microvascular invasive assessment by means of IMR, CFR and RRR	The incidence of CMD was higher in the TTS patients than in the INOCA cohort, with higher IMR, lower CFR, and lower RRR
Galiuto et al. [55]	15 female TTS patients 15 age and gender-matched STEMI patients	Myocardial contrast echocardiography at baseline and during adenosine infusion (140 μg/kg/min) within 5 days since symptoms onset and after 1-month	- No difference in myocardial perfusion and dysfunction was detected between the two groups at baseline. Adenosine infusion improved myocardial perfusion and LV function only in the TTS group - At 1-month follow-up, myocardial perfusion and dysfunction completely recovered only in TTS patients.
Dong et al. [60]	Murine models - Wild Type - Kv1.5 −/− - TgKv1.5 −/−	TAC was used to induce a hypertensive stress. LV function alterations were assessed with echocardiography and changes in genetic expression between the base and the apex of the LV were confirmed by RT-PCR	- Mice who developed TTS following TAC presented abnormalities in blood flow regulation between LV apex and base - Equalization of MBF between the apex and base through pharmacological coronary dilation with chromonar or genetic re-expression of Kv1.5 channels in smooth muscle eliminated regional differences in ventricular function

Abbreviations: CMD: coronary microvascular dysfunction; CFR: coronary flow reserve; IMR: index of microcirculatory; INOCA: ischemia with no obstructive coronary artery; LV: left ventricle; MBF: myocardial blood flow; RRR: resistive reserve ratio; RT-PCR: real time-polymerase chain reaction; STEMI: ST-elevation myocardial infarction; TAC: transaortic constriction; TTS: Takotsubo syndrome.

In conclusion this study suggests that abnormalities in flow regulation between the LV apex and the base may cause TTS, and maintaining equivalent MBF in the apex and base through pharmacological coronary dilation with chromonar or genetic re-expression of Kv1.5 channels in smooth muscle eliminates regional differences in ventricular function.

On the basis of these data, it is conceivable to conclude that TTS may be deemed an acute coronary microvascular syndrome strengthening the hypothesis of considering TTS as an ACS, clinical and laboratory presentation of TTS resembles an acute coronary event due to obstructive CAD in many cases and differentiating these entities may be sometimes difficult in clinical practice [66,67]. Recently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been proven to foster CMD through both an exaggerated systemic inflammatory response and direct microvessels invasion, thus making SARS-CoV-2 a novel potential trigger of conditions characterized by acute CMD, including TTS [68,69].

4. Takotsubo pathophysiology overview

A schematic illustration of TTS pathophysiology in provided in Fig. 1. Putting together the pieces, TTS is elicited by a trigger (e.g. physically or emotionally stressful event, pheochromocytoma, acute brain disorders, drugs) acting on a pre-existing vulnerable soil (including oestrogen deficiency, limbic system alterations, genetic and epigenetic factors, inflammatory conditions) and causing sympathetic hyperactivity [70]. As a consequence, acute coronary microvascular spasm occurs and leads to myocardial dysfunction. There is evidence of a concomitant direct catecholaminergic myocardial damage, which however is unlikely to be relevant considering the typical absence of late gadolinium enhancement at CMR in this population [14,71]. Accordingly, the early cardiac function restoration in over 80% of cases is indeed explained by the fact that microvascular spasm activates the same survival pathways as hibernation, thus preventing cardiomyocytes from necrosis and consequent myocardial scarring [4,65].

5. Gaps in knowledge and future perspectives

Accumulating evidence suggests that an acute microvascular dysfunction plays a key role in the pathogenesis of TTS (Table 1). A possible challenge to the notion that TTS is an ACS due to an acute CMD could be that, in consideration of the high prevalence of CMD (with estimates ranging from 40% in non-obstructive coronary artery disease [NOCAD] and up to 75% in patients with HFpEF), a higher incidence of TTS would be expected, while TTS accounts for only the 2% of all ACS [72,73]. However, it is important to underline that CMD and TTS should

be deemed different parts of the same continuum, with TTS representing an abrupt manifestation of CMD, essentially an acute microcirculatory syndrome, in the presence of predisposing factors.

However, in some studies CMD was not detected in all patients [58]. A probable explanation for this finding may be that microvascular impairment is typically transient in this syndrome and might have had already resolved in some patients at the moment of the evaluation. For this reason, the timing of CMD assessment TTS patients is crucial in order to get reliable results and should be standardized in future studies.

The main impact of this reappraisal of TTS pathogenesis may have important therapeutic consequences. Indeed, the development of targeted therapies aimed to reverse coronary microvascular spam may reduce the incidence of in-hospital complications and long-term consequences. At present, there are only few proof-of-concept studies investigating the use of microvascular vasodilators, such as adenosine and chromonar [59,65]. Large randomized clinical trials are warranted to confirm the benefit of these drugs in TTS patients.

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References

[1] H. Medina de Chazal, M.G. Del Buono, L. Keyser-Marcus, et al., Stress cardiomyopathy diagnosis and treatment: JACC state-of-the-art review, J. Am. Coll. Cardiol. 72 (2018) 1955–1971.
[2] H. Sato, H. Tateishi, T. Uchida, et al., Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm, in: Clinical Aspects of Myocardial Injury: From Ischemia to Heart Failure, Kagakuhyoronsha Publishing, Tokyo, 1990, pp. 56–64.
[3] K. Tsuchihashi, K. Ueshima, T. Uchida, et al., Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan, J. Am. Coll. Cardiol. 38 (2001) 11–18.
[4] J.R. Ghadri, I.S. Wittstein, A. Prasad, et al., International expert consensus document on Takotsubo syndrome (part II): diagnostic workup, outcome, and management, Eur. Heart J. 39 (2018) 2047–2062.
[5] M.G. Del Buono, R.A. Montone, G. Iannaccone, M.C. Meucci, R. Rinaldi, D. D'Amario, et al., Diagnostic work-up and therapeutic implications in MINOCA: need for a personalized approach, Futur. Cardiol. 17 (2021 Jan) 149–154.
[6] C. Templin, J.R. Ghadri, J. Diekmann, et al., Clinical features and outcomes of Takotsubo (stress) cardiomyopathy, N. Engl. J. Med. 373 (2015) 929–938.
[7] M.G. Del Buono, R.A. Montone, M.C. Meucci, G. La Vecchia, M. Camilli, L. Giraldi, et al., Left ventricular end-diastolic pressure predicts in-hospital outcomes in takotsubo syndrome, Eur. Heart J. Acute Cardiovasc. Care 10 (2021 Aug 24) 661–667.
[8] R.A. Montone, G. La Vecchia, M.G. Del Buono, A. Abbate, T. Sanna, D. Pedicino, et al., Takotsubo syndrome in intensive cardiac care unit: challenges in diagnosis and management, Curr. Probl. Cardiol. 47 (2022 Nov) 101084.
[9] K. Gonuguntla, H. Thyagaturu, A. Shaik, N. Roma, S. Thangjui, W. Alruwaili, et al., Takotsubo cardiomyopathy and psychiatric illness- insight from National Inpatient Sample (NIS) and National re-admission Database (NRD) 2016 to 2018, Curr. Probl. Cardiol. 49 (2024 Feb 6) 102429.
[10] I.S. Wittstein, D.R. Thiemann, J.A. Lima, K.L. Baughman, S.P. Schulman, G. Gerstenblith, et al., Neurohumoral features of myocardial stunning due to sudden emotional stress, N. Engl. J. Med. 352 (2005 Feb 10) 539–548.
[11] Y-Hassan S., Plasma epinephrine level and its causal link to Takotsubo syndrome revisited: critical review with a diverse conclusion, Cardiovasc. Revasc. Med. 20 (2019 Oct) 907–914.
[12] T. Kume, T. Kawamoto, H. Okura, E. Toyota, Y. Neishi, N. Watanabe, et al., Local release of catecholamines from the hearts of patients with Tako-tsubo-like left ventricular dysfunction, Circ. J. 72 (2008) 106–108.
[13] K. Osuala, K. Telusma, S.M. Khan, S. Wu, M. Shah, C. Baker, S. Alam, et al., Distinctive left-sided distribution of adrenergic-derived cells in the adult mouse heart, PLoS One 6 (2011) e22811.
[14] A.R. Lyon, R. Citro, B. Schneider, O. Morel, J.R. Ghadri, C. Templin, et al., Pathophysiology of Takotsubo syndrome: JACC state-of-the-art review, J. Am. Coll. Cardiol. 77 (2021 Feb 23) 902–921.
[15] C. Templin, J. Hänggi, C. Klein, M.S. Topka, T. Hiestand, R.A. Levinson, et al., Altered limbic and autonomic processing supports brain-heart axis in Takotsubo syndrome, Eur. Heart J. 40 (15) (2019).
[16] T. Hiestand, J. Hänggi, C. Klein, M.S. Topka, M. Jaguszewski, J.R. Ghadri, et al., Takotsubo syndrome associated with structural brain alterations of the limbic system, J. Am. Coll. Cardiol. 71 (2018 Feb 20) 809–811.
[17] A. Radfar, S. Abohashem, M.T. Osborne, Y. Wang, T. Dar, M.Z.O. Hassan, et al., Stress-associated neurobiological activity associates with the risk for and timing of subsequent Takotsubo syndrome, Eur. Heart J. 42 (19) (2021).
[18] H. Suzuki, K. Takanami, K. Takase, H. Shimokawa, S. Yasuda, Reversible increase in stress-associated neurobiological activity in the acute phase of Takotsubo syndrome; a brain 18F-FDG-PET study, Int. J. Cardiol. 344 (2021 Dec 1) 31–33.
[19] T. Stiermaier, F. Santoro, I. El-Battrawy, C. Möller, T. Graf, G. Novo, et al., Prevalence and prognostic impact of diabetes in Takotsubo syndrome: insights from the international, multicenter GEIST registry, Diabetes Care 41 (2018 May) 1084–1088.
[20] V. Bill, I. El-Battrawy, M. Behnes, S. Baumann, T. Becher, E. Elmas, et al., "Diabetes paradox" in Takotsubo cardiomyopathy, Int. J. Cardiol. 224 (2016 Dec 1) 88–89.
[21] R.A. Montone, G. Niccoli, M.G. Del Buono, L. Galiuto, F. Crea, Special article - emotional versus physical Takotsubo syndrome: two faces of the same medal or two different syndromes? Prog. Cardiovasc. Dis. 63 (2020 Sep-Oct) 699–701.
[22] C. Vitale, M.E. Mendelsohn, G.M. Rosano, Gender differences in the cardiovascular effect of sex hormones, Nat. Rev. Cardiol. 6 (2009 Aug) 532–542.
[23] R. Li, Y. Shen, Estrogen and brain: synthesis, function and diseases, Front. Biosci. 10 (2005 Jan 1) 257–267.
[24] T. Ueyama, F. Ishikura, A. Matsuda, T. Asanuma, K. Ueda, M. Ichinose, et al., Chronic estrogen supplementation following ovariectomy improves the emotional stress-induced cardiovascular responses by indirect action on the nervous system and by direct action on the heart, Circ. J. 71 (2007 Apr) 565–573.
[25] A. Thawornkaiwong, S. Preawnim, J. Wattanapermpool, Upregulation of beta 1-adrenergic receptors in ovariectomized rat hearts, Life Sci. 72 (2003 Mar 7) 1813–1824.
[26] J.C. Kaski, Cardiac syndrome X in women: the role of oestrogen deficiency, Heart. 92 (Suppl. 3) (2006 May) iii5-9.
[27] P. Collins, G.M. Rosano, P.M. Sarrel, L. Ulrich, S. Adamopoulos, C.M. Beale, J. G. McNeill, et al., 17 beta-estradiol attenuates acetylcholine-induced coronary arterial constriction in women but not men with coronary heart disease, Circulation. 92 (1995 Jul 1) 24–30.
[28] A.H. Chester, C. Jiang, J.A. Borland, M.H. Yacoub, P. Collins, Oestrogen relaxes human epicardial coronary arteries through non-endothelium-dependent mechanisms, Coron. Artery Dis. 6 (1995 May) 417–422.
[29] G. Iannaccone, R.A. Montone, M.G. Del Buono, M.C. Meucci, R. Rinaldi, F. L. Gurgoglione, et al., Recurrent asymptomatic Takotsubo syndrome after 20 years: are we looking at the tip of the iceberg only? Futur. Cardiol. 17 (2021 Mar) 309–314.
[30] C. Fernández-Cordón, I.J. Núñez-Gil, I. Martín de Miguel, A. Pérez-Castellanos, O. Vedia, M. Almendro-Delia, et al., Takotsubo syndrome, stressful triggers, and risk of recurrence, Am. J. Cardiol. 205 (2023 Oct 15) 58–62.
[31] M.R. Burg, T. Felice, M. Caruana, M.A. Sammut, Like mother like daughter: a case report of simultaneous mother-daughter Takotsubo cardiomyopathy triggered by a house fire, Int. J. Cardiol. 220 (2016 Oct 1) 312–313.
[32] A.H. Goodloe, J.M. Evans, S. Middha, A. Prasad, T.M. Olson, Characterizing genetic variation of adrenergic signalling pathways in Takotsubo (stress) cardiomyopathy exomes, Eur. J. Heart Fail. 16 (2014 Sep) 942–949.
[33] S.W. Sharkey, B.J. Maron, P. Nelson, M. Parpart, M.S. Maron, M.R. Bristow, Adrenergic receptor polymorphisms in patients with stress (tako-tsubo) cardiomyopathy, J. Cardiol. 53 (2009 Feb) 53–57.
[34] O. Vriz, R. Minisini, R. Citro, V. Guerra, C. Zito, G. De Luca, et al., Analysis of beta1 and beta2-adrenergic receptors polymorphism in patients with apical ballooning cardiomyopathy, Acta Cardiol. 66 (2011 Dec) 787–790.
[35] L. Spinelli, V. Trimarco, S. Di Marino, M. Marino, G. Iaccarino, B. Trimarco, L41Q polymorphism of the G protein coupled receptor kinase 5 is associated with left ventricular apical ballooning syndrome, Eur. J. Heart Fail. 12 (2010 Jan) 13–16.
[36] G. Novo, S. Giambanco, M. Guglielmo, L. Arvigo, M.R. Sutera, F. Giambanco, et al., G-protein-coupled receptor kinase 5 polymorphism and Takotsubo cardiomyopathy, J. Cardiovasc. Med. (Hagerstown) 16 (2015 Sep) 639–643.
[37] G.A. Figtree, R.D. Bagnall, I. Abdulla, S. Buchholz, K.K. Galougahi, W. Yan, et al., No association of G-protein-coupled receptor kinase 5 or β-adrenergic receptor polymorphisms with Takotsubo cardiomyopathy in a large Australian cohort, Eur. J. Heart Fail. 15 (2013 Jul) 730–733.
[38] O. Vriz, R. Minisini, C. Zito, E. Boccato, F. Fimiani, M. Pirisi, et al., Can apical ballooning cardiomyopathy and anterior STEMI be differentiated based on β1 and β2-adrenergic receptors polymorphisms? Int. J. Cardiol. 199 (2015 Nov 15) 189–192.

[39] H.M. Nef, H. Möllmann, C. Troidl, S. Kostin, T. Böttger, S. Voss, et al., Expression profiling of cardiac genes in Tako-Tsubo cardiomyopathy: insight into a new cardiac entity, J. Mol. Cell. Cardiol. 44 (2008 Feb) 395–404.
[40] G. Pizzino, A. Bitto, P. Crea, B. Khandheria, O. Vriz, S. Carerj, et al., Takotsubo syndrome and estrogen receptor genes: partners in crime? J. Cardiovasc. Med. (Hagerstown) 18 (2017 Apr) 268–276.
[41] G. Limongelli, D. Masarone, V. Maddaloni, M. Rubino, F. Fratta, A. Cirillo, S. B. Ludovica, R. Pacileo, A. Fusco, G.R. Coppola, F. Pisacane, E. Bossone, P. Calabrò, R. Calabrò, M.G. Russo, G. Pacileo, Genetics of Takotsubo Syndrome, Heart Fail Clin 12 (4) (2016) 499–506, https://doi.org/10.1016/j.hfc.2016.06.007.
[42] C.J. Lacey, K. Doudney, P.G. Bridgman, P.M. George, R.T. Mulder, J.J. Zarifeh, et al., Copy number variants implicate cardiac function and development pathways in earthquake-induced stress cardiomyopathy, Sci. Rep. 8 (2018 May 15) 7548.
[43] H. Keller, U. Neuhold, F. Weidinger, E. Gatterer, C. Stöllberger, K. Huber, et al., Takotsubo as initial manifestation of non-myopathic cardiomyopathy due to the titin variant c.1489G > T, Medicines (Basel). 5 (2018 Jul 30) 80.
[44] I. Khurana, S. Maxwell, S. Royce, P. Mathiyalagan, T. Karagiannis, N. Mazarakis, et al., SAHA attenuates Takotsubo-like myocardial injury by targeting an epigenetic Ac/Dc axis, Signal Transduct. Target. Ther. 6 (2021 Apr 20) 159.
[45] M. Jaguszewski, J. Osipova, J.R. Ghadri, L.C. Napp, C. Widera, J. Franke, et al., A signature of circulating microRNAs differentiates takotsubo cardiomyopathy from acute myocardial infarction, Eur. Heart J. 35 (2014 Apr) 999–1006.
[46] L.S. Couch, J. Fiedler, G. Chick, R. Clayton, E. Dries, L.M. Wienecke, et al., Circulating microRNAs predispose to takotsubo syndrome following high-dose adrenaline exposure, Cardiovasc. Res. 118 (2022 Jun 22) 1758–1770.
[47] M. Bai, X. Zhu, Y. Zhang, S. Zhang, L. Zhang, L. Xue, et al., Abnormal hippocampal BDNF and miR-16 expression is associated with depression-like behaviors induced by stress during early life, PLoS One 7 (2012) e46921.
[48] V.R. Enatescu, I. Papava, I. Enatescu, M. Antonescu, A. Anghel, E. Seclaman, et al., Circulating plasma Micro RNAs in patients with major depressive disorder treated with antidepressants: a pilot study, Psychiatry Investig. 13 (2016 Sep) 549–557.
[49] F. Santoro, N. Tarantino, A. Ferraretti, R. Ieva, F. Musaico, F. Guastafierro, et al., Serum interleukin 6 and 10 levels in Takotsubo cardiomyopathy: increased admission levels may predict adverse events at follow-up, Atherosclerosis. 254 (2016 Nov) 28–34.
[50] R.J. Raymond, G.J. Dehmer, T.C. Theoharides, E.N. Deliargyris, Elevated interleukin-6 levels in patients with asymptomatic left ventricular systolic dysfunction, Am. Heart J. 141 (2001 Mar) 435–438.
[51] T. Tsutamoto, T. Hisanaga, A. Wada, K. Maeda, M. Ohnishi, D. Fukai, et al., Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure, J. Am. Coll. Cardiol. 31 (1998 Feb) 391–398.
[52] F. Santoro, M.D. Costantino, F. Guastafierro, G. Triggiani, A. Ferraretti, N. Tarantino, et al., Inflammatory patterns in Takotsubo cardiomyopathy and acute coronary syndrome: a propensity score matched analysis, Atherosclerosis. 274 (2018 Jul) 157–161.
[53] I. Eitel, C. Lücke, M. Grothoff, M. Sareban, G. Schuler, H. Thiele, et al., Inflammation in takotsubo cardiomyopathy: insights from cardiovascular magnetic resonance imaging, Eur. Radiol. 20422-31 (2010 Feb).
[54] W. Lin, S.H. Tay, A. Mak, Takotsubo syndrome and rheumatic diseases-a critical systematic review, Rheumatology (Oxford) 60 (1) (2021) 11–22, https://doi.org/10.1093/rheumatology/keaa504.
[55] R. Pirzer, E. Elmas, D. Haghi, C. Lippert, S. Kralev, S. Lang, et al., Platelet and monocyte activity markers and mediators of inflammation in Takotsubo cardiomyopathy, Heart Vessel. 27 (2012 Mar) 186–192.
[56] D.K. Dawson, C.J. Neil, A. Henning, D. Cameron, B. Jagpal, M. Bruce, et al., TakoTsubo cardiomyopathy: a heart stressed out of energy? JACC Cardiovasc. Imaging 8 (2015) 985–987.
[57] K. Schwarz, T. Ahearn, J. Srinivasan, C.J. Neil, C. Scally, A. Rudd, et al., Alterations in cardiac deformation, timing of contraction and relaxation, and early myocardial fibrosis accompany the apparent recovery of acute stress-induced (takotsubo) cardiomyopathy: an end to the concept of transience, J. Am. Soc. Echocardiogr. 30 (2017) 745–755.
[58] S. Y-Hassan, Coronary microvascular dysfunction in Takotsubo syndrome: cause or consequence, Am. J. Cardiovasc. Dis. 11 (2021 Apr 15) 184–193. PMID: 34084653; PMCID: PMC8166587.
[59] L. Galiuto, A.R. De Caterina, A. Porfidia, L. Paraggio, S. Barchetta, G. Locorotondo, et al., Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in Apical Ballooning or Tako-Tsubo Syndrome, Eur. Heart J. 31 (2010 Jun) 1319–1327.
[60] H. Mori, S. Ishikawa, S. Kojima, J. Hayashi, Y. Watanabe, J.I. Hoffman, et al., Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli, Cardiovasc. Res. 27 (1993 Feb) 192–198.
[61] I. Eitel, F. von Knobelsdorff-Brenkenhoff, P. Bernhardt, I. Carbone, K. Muellerleile, A. Aldrovandi, et al., Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy, JAMA 306 (2011 Jul) 277–286.
[62] R.A. Montone, L. Galiuto, M.C. Meucci, et al., Coronary slow flow is associated with a worse clinical outcome in patients with Takotsubo syndrome, Heart. 106 (2020) 923–930.
[63] M. Loffi, A. Santangelo, M. Kozel, et al., Takotsubo cardiomyopathy: one more angiographic evidence of microvascular dysfunction, Biomed. Res. Int. 2018 (2018) 5281485.
[64] C. Ekenbäck, J. Nickander, F. Jokhaji, P. Tornvall, H. Engblom, J. Spaak, et al., Coronary microvascular dysfunction in Takotsubo syndrome and associations with left ventricular function, ESC Heart Fail. 10 (2023 Aug) 2395–2405.
[65] F. Dong, L. Yin, H. Sisakian, T. Hakobyan, L.S. Jeong, H. Joshi, et al., Takotsubo syndrome is a coronary microvascular disease: experimental evidence, Eur. Heart J. 44 (2023 Jun 25) 2244–2253.
[66] F. Crea, R.A. Montone, R. Rinaldi, Pathophysiology of coronary microvascular dysfunction, Circ. J. 86 (2022 Aug 25) 1319–1328.
[67] R.A. Montone, I.K. Jang, J.F. Beltrame, R. Sicari, M.C. Meucci, M. Bode, et al., The evolving role of cardiac imaging in patients with myocardial infarction and non-obstructive coronary arteries, Prog. Cardiovasc. Dis. 68 (2021 Sep-Oct) 78–87.
[68] R.A. Montone, G. Iannaccone, M.C. Meucci, F. Gurgoglione, G. Niccoli, Myocardial and microvascular injury due to coronavirus disease 2019, Eur. Cardiol. 15 (2020 Jun 23) e52.
[69] M.P. Nägele, B. Haubner, F.C. Tanner, F. Ruschitzka, A.J. Flammer, Endothelial dysfunction in COVID-19: current findings and therapeutic implications, Atherosclerosis. 314 (2020 Dec) 58–62.
[70] F. Pelliccia, J.C. Kaski, F. Crea, P.G. Camici, Pathophysiology of Takotsubo syndrome, Circulation. 135 (2017 Jun 13) 2426–2441.
[71] R. Citro, H. Okura, J.R. Ghadri, C. Izumi, P. Meimoun, M. Izumo, et al., Multimodality imaging in takotsubo syndrome: a joint consensus document of the European Association of Cardiovascular Imaging (EACVI) and the Japanese Society of Echocardiography (JSE), J. Echocardiogr. 18 (2020 Dec) 199–224.
[72] M.G. Del Buono, R.A. Montone, M. Camilli, S. Carbone, J. Narula, C.J. Lavie, et al., Coronary microvascular dysfunction across the Spectrum of cardiovascular diseases: JACC state-of-the-art review, J. Am. Coll. Cardiol. 78 (2021 Sep 28) 1352–1371.
[73] D. D'Amario, S. Migliaro, J.A. Borovac, A. Restivo, R. Vergallo, M. Galli, et al., Microvascular dysfunction in heart failure with preserved ejection fraction, Front. Physiol. 10 (2019 Nov 5) 1347.